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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/715,902	11/17/2000	John James Donnelly	1627.003	5612

27476 7590 10/06/2008

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ART UNIT	PAPER NUMBER
1633	

MAIL DATE	DELIVERY MODE
10/06/2008	PAPER

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BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Application Number: 09/715,902
Filing Date: November 17, 2000
Appellant(s): DONNELLY ET AL.

David B. Bonham
For Appellant

EXAMINER'S ANSWER

This is in response to the appeal brief filed 5/17/07 appealing from the Office action mailed 11/2/05.

(1) Real Party in Interest

A statement identifying by name the real party in interest is contained in the brief.

(2) Related Appeals and Interferences

The examiner is not aware of any related appeals, interferences, or judicial proceedings which will directly affect or be directly affected by or have a bearing on the Board's decision in the pending appeal.

(3) Status of Claims

The statement of the status of claims contained in the brief is correct.

(4) Status of Amendments After Final

No amendment to the claims after final has been filed.

(5) Summary of Claimed Subject Matter

The summary of claimed subject matter contained in the brief is correct.

(6) Grounds of Rejection to be Reviewed on Appeal

The appellant's statement of the grounds of rejection to be reviewed on appeal is correct.

(7) Claims Appendix

The copy of the appealed claims contained in the Appendix to the brief is correct.

(8) Evidence Relied Upon

WO 97/24447 (SONG et al.) 10 July 1997.

US Patent No. 5,783,567 (HEDLEY et al.) 21 July 1998.

Fattal et al. (1998) J. Controlled Rel., Vol. 53, 137-143

Yang et al. (1999) Int. J. Cancer, Vol. 83, 532-54

Manickan et al. (1997) J. Leuk. Biol., Vol. 61, 125-132

Spahn et al. (1996) Proc. Am. Assoc. Canc. Res., Vol. 37, 486-487

Tuting et al. (1998) J. Immunol., Vol. 160, 1139-1147

(9) Grounds of Rejection

The following ground(s) of rejection are applicable to the appealed claims:

Claims 1-16, 18-23, 29-31, 33-44, 46, 50, and 52-54 stand rejected under 35 U.S.C. 103(a) as being unpatentable over WO 97/24447 (7/10/97), hereafter referred to as Song et al., in view of US Patent No. 5,783,567 (7/21/98), hereafter referred to as Hedley et al., and further in view of Fattal et al. (1998) J. Controlled Rel., Vol. 53, 137-143.

Song et al. teaches methods of transfecting dendritic cells *ex vivo* or *in vitro* with a gene delivery vehicle comprising DNA encoding an antigen such as a tumor antigen, a viral antigen and specifically an HIV antigen, or an antigen derived from fungi, parasites, or bacteria, and use of said transfected dendritic cells to induce an immune response against the expressed antigen *in vivo* (Song et al., pages 2, 3, and 18-20). Song et al. teaches that the transfected dendritic cells

can be administered to a vertebrate parenterally or by direct injection, and that the dendritic cells can be derived from bone marrow and cultured for at least 7 days prior to transfection (Song et al., pages 26 and 39). Song et al. also teaches wherein the DNA encoding an antigen is a plasmid DNA (Song et al., page 18).

Song et al. differs from the instant invention by not specifically teaching the use of the combination of polynucleotides, biodegradable polymers, and cationic detergents as a gene delivery vehicle for dendritic cells. Song et al. however does teach that numerous gene delivery vehicles can be successfully utilized to transfect dendritic cells including the use of plasmid/liposomes and specifically cationic liposomes, and plasmid combined with cationic condensing agents (Song et al., pages 3 and 18). Hedley et al. supplements Song et al. by teaching the use of microspheres comprising biodegradable polymers and DNA plasmids to introduce and express antigens encoded by the plasmids in antigen presenting cells such as macrophages and dendritic cells both *in vitro* and *in vivo* for the purpose of stimulating antigen specific immune responses (Hedley et al., columns 2-3 and 7-8). Hedley et al. further teaches that numerous biodegradable polymers and copolymers can be used to form the microspheres including poly(lactide) and poly (caprolactone) (Hedley et al., columns 10-11). As a preferred embodiment, Hedley et al. teaches the use of the copolymer (D, L-lactide-co-glycolide) (Hedley et al., column 11). Hedley et al. further teaches the preparation of microparticles comprising plasmid DNA which have an average size of between 1-10 um, but which include microparticles of "about" 500 nm as well, where the plasmid DNA is mostly encapsulated in the microparticle (Hedley et al., column 14 and Figure 2). Hedley et al. further provides motivation for introducing plasmid DNA encoding an antigen to dendritic cells and macrophages by teaching that DNA

combined with biodegradable microparticles is efficiently phagocytosed by APCs and is an effective means for introducing nucleic acids into these cells (Hedley et al., column 8, lines 13-49). Thus, based on the motivation to introduce nucleic acids into macrophages and dendritic cells using biodegradable polymers as taught by Hedley et al., it would have been *prima facie* obvious to the skilled artisan to use biodegradable particles and plasmid DNA as the gene delivery vehicle in the methods of transfecting dendritic cells and methods of immunizing taught by Song et al. Further, based on the efficiency of phagocytosis of biodegradable particles taught by Hedley et al., the skilled artisan would have had a reasonable expectation of success in using biodegradable particles to deliver polynucleotides to dendritic cells *in vitro* or *in vivo*.

Both Song et al. and Hedley et al. differ from the instant invention in that they do not teach that use of microparticles containing a cationic detergent, where the polynucleotide is adsorbed to the surface of the particles, to transfect dendritic cells. Fattal et al. teaches that the association of oligonucleotides with particles comprised of biodegradable polymers is increased by the addition of cationic detergents such as CTAB, and which further allows for adsorption of the polynucleotide to the nanoparticles (Fattal et al., pages 137 and 139, Figure 1). Fattal et al. further reports an increase in phagocytosis/endocytosis of nanoparticles of "about" 500nm made using a cationic detergent (Fattal et al., page 137). Thus, Fattal et al. provides motivation for including a cationic detergent such as CTAB in the preparation of transfection agents comprising biodegradable polymers and polynucleotides in order to increase the amount of polynucleotide associated with the polymer particles and increase the uptake of the microparticles by phagocytosis. Therefore, in view of the motivation provided by Fattal et al. discussed above, and the teachings of Song et al. that cationic reagents are effective in delivery expressible plasmids to

dendritic cells, it would have been *prima facie* obvious to the skilled artisan at the time of filing to include a cationic detergent in a gene delivery vehicle comprising biodegradable polymers in order to increase the association of polynucleotide with the particle and to increase phagocytosis by the target cell. Further, the skilled artisan would have had a reasonable expectation of making and using a transfection agent comprising a polynucleotide both adsorbed onto and encapsulated within biodegradable polymer particles comprising a cationic detergent to transfect dendritic cells based on the successful use of oligonucleotide nanoparticles comprising biodegradable polymer and CTAB taught by Fattal et al. to transfect cells *in vitro* and *in vivo*, the high degree of skill in the art of molecular biology and cell biology at the time of filing, and the state of the art for transfecting dendritic cells with expressible non-viral polynucleotides including the use of cationic particles and reagents as taught by Song et al.

(10) Response to Argument

The appellant has split their response to the rejection of claims 1-16, 18-23, 29-31, 33-44, 46, 50, and 52-54 set forth above into three parts. The appellant has chosen to provide separate argument sections for 1) claim 54, 2) claims 1-16, 18-23, 29-31, 33-34, 46, 50, and 52-53, and 3) claims 19-23. However, please note that claims 19-23 have been argued twice in separate sections. These arguments are addressed in order.

1) The appellant argues that claim 54 is non-obvious and alleges that the rejection of record is based on improper hindsight reasoning, citing MPEP 2141-2142, *In re Vaeck* and

Hodosh v. Block Drug Co., Inc. The appellant then points out what, in appellant's opinion, are the deficiencies in each reference that precludes their combination.

To begin, it is noted that the test for combining references is not what the individual references themselves suggest, but rather what the combination of disclosures taken as a whole would have suggested to one of ordinary skill in the art. *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971). For the purpose of combining references, those references need not explicitly suggest combining teachings, much less specific references. *In re Nilssen*, 7 USPQ2d 1500 (Fed. Cir. 1988). Furthermore, it is well established in case law that a reference must be considered not only for what it expressly teaches, but also for what it fairly suggests. *In re Burkel*, 201 USPQ 67 (CCPA 1979). In the determination of obviousness, the state of the art as well as the level of skill of those in the art are important factors to be considered. The teaching of the cited references must be viewed in light of these factors. Most importantly, obviousness does **not** require absolute predictability of success; for obviousness under 35 U.S.C. 103, all that is required is a reasonable expectation of success. See *In re O'Farrell*, 7 USPQ2d 1673 (CAFC 1988). Further, in response to Appellant's argument that the examiner's conclusion of obviousness is based upon improper hindsight reasoning, it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the Appellant's disclosure, such a reconstruction is proper. See *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971).

The Appellant acknowledges that Song et al. teaches several gene delivery vehicles for gene livery to dendritic cells, but argues that Song et al. does not teach a transfection agent comprising a polynucleotide and a microparticle as claimed, and that Song et al. demonstrates a preference for recombinant retroviral techniques over non-viral techniques. The Appellant further argues that neither Hedley et al. nor Fattal et al. overcome this deficiency in Song. As such, the Appellant concludes that Song et al. in combination with the other cited references would only provide motivation for using recombinant retroviruses for *in vivo* transfection of dendritic cells. In response, Song et al. teaches methods of transfecting dendritic cells *ex vivo* or *in vitro* with a gene delivery vehicle comprising DNA encoding an antigen such as a tumor antigen or HIV antigen, and use of said transfected dendritic cells to induce an immune response against the expressed antigen in vivo (Song et al., pages 2, 3, and 18-20). Regarding gene delivery vehicles taught by Song et al., Song teaches that for *ex vivo/in vitro* transfection of dendritic cells, both non-viral and viral gene delivery vehicles can be used, including the use of expression vectors complexed with polycations or lipids, or encapsulated in liposomes (Song et al., page 1, and pages 14-19). Thus, Song et al. teaches that numerous gene delivery vehicles can be successfully utilized to transfect dendritic cells including the use of plasmid/liposomes, and plasmid combined with cationic condensing agents. The fact that Song et al. exemplified retroviral transduction of dendritic cells does not invalidate the clear teachings in this reference that many techniques, including non-viral techniques, can be used to transfect dendritic cells *in vitro*. According to the Appellants, the fact that Song et al. exemplified retroviruses teaches away from using non-viral vectors. However, this is not a fair reading of Song et al., as Song et al. clearly teaches the use of other delivery vectors, specifically non-viral vectors. Again, a

reference must be considered not only for what it expressly teaches, but also for what it fairly suggests. *In re Burkel*, 201 USPQ 67 (CCPA 1979). Further, the appellant is directed to *In re Susi* and *In re Gurley*, which state respectively: that disclosed examples and preferred embodiments do not constitute a teaching away from a broader disclosure or nonpreferred embodiments. *In re Susi*, 440 F.2d 442, 169 USPQ 423 (CCPA 1971); and, "A known or obvious composition does not become patentable simply because it has been described as somewhat inferior to some other product for the same use." *In re Gurley*, 27 F.3d 551, 554, 31 USPQ2d 1130, 1132 (Fed. Cir. 1994). Thus, the office does not find that Song et al. teaches away from using non-viral vectors simply because they exemplified the use of the retroviral vectors rather than the use of the disclosed non-viral vectors. Furthermore, the Appellant is reminded that claim 54 as written, does not place any limitation on the nature of the polynucleotide and reads on the use of any polynucleotide including a retroviral polynucleotide.

In regards to Appellant's argument that Song et al. does not teach the use of microparticles, it is noted that Hedley et al. and Fattal et al. have been cited to supplement the teachings of Song et al. Regarding the teachings of Hedley et al., the Appellant argues that Hedley primarily teaches the use of microparticles to transfect macrophages and that the only motivation for transfecting dendritic cells lies in *in vivo* rather than *in vitro/ex vivo* techniques. The appellant therefore concludes that the Office has engaged in improper hindsight reasoning to construct the rejection of record. In response, Hedley et al. has been cited for the use of microspheres comprising biodegradable polymers and DNA plasmids to introduce and express antigens encoded by the plasmids in antigen presenting cells such as macrophages and dendritic cells both *in vitro* and *in vivo* for the purpose of stimulating antigen specific immune responses

(Hedley et al., columns 2-3 and 7-8). The fact that Hedley et al. teaches that transfection can take place *in vivo*, does not teach away from the clear suggestion to transfect cells *in vitro/ex vivo* taught by Hedley et al. in column 12. Hedley et al. further provides motivation for introducing plasmid DNA encoding an antigen to dendritic cells and macrophages using biodegradable microspheres by teaching that DNA combined with biodegradable microparticles is efficiently phagocytosed by antigen presenting cells (APCs) and is an effective means for introducing nucleic acids into these cells (Hedley et al., column 8, lines 13-49). While Hedley exemplifies the transfection of macrophages, the teachings of Hedley et al. are not so limited. Hedley et al. clearly teaches the transfection of APCs. Dendritic cells were well known at the time of filing as antigen presenting cells, as evidenced by Song et al. Further, Hedley et al. recognizes that dendritic cells are a legitimate target for the disclosed microparticle transfection when they state that the point of introduction of plasmid/microparticles to skin is the transfection of dendritic cells. Motivation for transfecting dendritic *ex vivo/in vitro* is derived primarily from the teachings of the primary reference, Song et al., who clearly teach and provide motivation for transfecting dendritic cells *ex vivo*, see above. However, Hedley et al. also teaches *ex vivo* transfection. In column 12, lines 23-30, Hedley et al. clearly states, "For in vitro/ex vivo use, the suspension of microparticles can be added either to cultured adherent mammalian cells or to a cell suspension". Thus, Hedley et al. clearly contemplates and teaches *ex vivo* transfection of APCs. This teaching is not limited to macrophages and includes other types of antigen presenting cells such as dendritic cells. Again, Song et al. already teaches the transfection of dendritic cells, Hedley is cited to provide motivation for using microparticles as a transfection agent. Thus,

Appellant's arguments that Hedley et al. only provide motivation for *in vivo* transfection of dendritic cells is not found persuasive.

Regarding the claim that improper hindsight has been used to construct the instant rejection, it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the Appellant's disclosure, such a reconstruction is proper. See *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971). Furthermore, although appellant has stated, "..it is a well settled tenant of patent law that '[t]he references must be considered as a whole and must suggest the desirability and thus the obviousness of making the combination'. MPEP 2141, citing *Hodosh v. BlockDrug Co., Inc.*, 786 F.2d 1136, 1143 n.5,229 USPQ 182, 187 n.5 (Fed. Cir. 1986). (Emphasis added.)", it is noted that MPEP 2141 has been updated to reflect the U.S. Supreme Court decision in *KSR International Co. v. Teleflex Inc. (KSR),* 550 U.S. ___, 82 USPQ2d 1385 (2007). MPEP 2141 now states that in part the KSR decision found that the Federal Courts had erred by overemphasizing "the risk of courts and patent examiners falling prey to hindsight bias" and as a result applying "[r]igid preventative rules that deny factfinders recourse to common sense" (Id.). Further, as discussed in detail above, improper hindsight was not used as Hedley et al. clearly contemplates and teaches *ex vivo* transfection of APCs. This teaching is not limited to macrophages and includes other types of antigen presenting cells such as dendritic cells, and Song et al. already teaches and provides specific motivation for *ex vivo/in vitro* transfection of dendritic cells.

The appellant then argues that Hedley et al. teaches microparticles with internal nucleic acids rather than microparticles with adsorbed polynucleotides as claimed in claim 54. In response, Fattal et al. was cited to supplement the teachings of Hedley et al. by providing motivation for including a cationic detergent in the microparticles. Regarding encapsulation versus adsorption, please note that claim independent 54, like independent claim 1, are both broad and encompass microparticles with both adsorbed and encapsulated nucleic acids. While appellant now argues that it is irrelevant what the claims might encompass since there must be a teaching or motivation present in the prior art to make a conclusion of obviousness, the appellant is first directed to MPEP 2141 which states that the first step in determining obviousness is a determination of the scope of the claimed invention. MPEP 2141, "[t]he scope of the claimed invention must be clearly determined by giving the claims the 'broadest reasonable interpretation consistent with the specification.' See *Phillips v. AWH Corp.,* 415 F.3d 1303, 1316, 75 USPQ2d 1321, 1329 (Fed. Cir. 2005) and MPEP § 2111.". The scope of claim 54, like that of claim 1, clearly encompasses polynucleotides both adsorbed and encapsulated by the microparticles. The appellant is directed to claims 46 and 50 in particular, which depend on claim 1, which specifically recite wherein a portion of the polynucleotide is entrapped within said microparticles. Thus, the scope of the claimed invention reads on microparticles which have polynucleotide absorbed to the surface and encapsulated within the particle. Further, the interaction of the polynucleotide with the microparticle depends on the charge characteristics of the microparticle itself and the presence or absence of additional molecules such as detergents or surfactants. The microparticles taught by Hedley et al. are not positively charged, thus combining the microparticles with the polynucleotide results primarily in encapsulation. On the other hand,

Fattal et al. clearly teaches that adding a cationic detergent to the biodegradable microparticles results in particles with a positive charge such that the majority of the negatively charged polynucleotide absorbs onto the cationic surface rather than encapsulating within. Fattal et al. provides a useful diagram of the interactions on page 139, Figure 1. Combining the teachings of Song et al., Hedley et al., and Fattal et al. would thus result in microparticles with primarily adsorbed polynucleotide on the surface of the particle. Motivation for combining the teachings of Fattal et al. with those of Song et al. and Hedley et al., rests in the teachings of Fattal et al. that inclusion of a cationic detergent in microparticles increases the amount of polynucleotide associated with the polymer particles and increases the uptake of the nucleic acid by phagocytosis.

The appellant further argues that the processes for preparing the microparticles of Hedley et al. and the cationic particles of Fattal et al. are non-analogous such that the skilled artisan would not draw inferences between the teachings of Song, Hedley and Fattal. Specifically, the appellant argues that although some ordinary artisans at the time of filing favored "..encapsulation based on the notion that the DNA would be protected from the destructive elements (e.g., nucleases) encountered in the biological milieu, and others favor[ed] adsorption based on the notion that the DNA would be protected from destructive elements (e.g., high shear stresses) encountered in the processing environment", the ordinary artisan would not have looked to Fattal et al. since Hedley already taught by method which avoided an adverse affect on nucleic acid integrity during the encapsulation process (see page 9 of the Appeal Brief). This argument is not persuasive since 1) both the techniques of Hedley et al. and Fattal et al. are clearly analogous as being drawn to the same purpose of particle-mediated transfection of cells with a

polynucleotide, and 2) by appellant's own admission, the prior art teaches that both methods have their advantages such that the substitution of one method for another would represent nothing more than simple substitution of one known method for another with predictable results. See MPEP 2141 Rationale (b), and *KSR International Co. v. Teleflex Inc. (KSR),* 550 U.S. ___, 82 USPQ2d 1385 (2007). Further, as noted above, Fattal et al. provides specific motivation for utilizing their methodology over Hedley's by teaching that inclusion of a cationic detergent in microparticles increases the amount of polynucleotide associated with the polymer particles and increases the uptake of the nucleic acid by phagocytosis.

Next, the appellant argues that Fattal et al. teaches antisense oligonucleotide rather than plasmid DNA such there would be no reasonable expectation of success in making and using CTAB microparticles adsorbed with plasmid DNA to transfect dendritic cells resulting in the expression of an encoded protein. This is not agreed. Figure 1 of Fattal et al. clearly demonstrates the chemical interaction between the oligonucleotide and the cationic microparticle. According to Fattal et al., it is the negatively charged phosphate groups of the nucleic acid chain that form ion pairs with the hydrophobic cations on the surface of the biodegradable microparticles (Fattal et al., page 139, column 1). Regardless of whether the nucleic acid is an antisense oligonucleotide or nucleic acid present in a DNA plasmid, the nature of nucleic acids is that the backbone of the molecule is negatively charged. Thus, based on the nature of the negatively charged phosphate groups present in all nucleic acids, the skilled artisan would have had reasonable expectation that negatively charged plasmid DNA would likewise form ion pairs with CTAB or another cationic detergent and would thus be capable of use in the microparticle/CTAB delivery vehicle taught by Fattal et al.. Appellant's argument that the skilled

artisan would not have been motivated to absorb plasmid DNA to microparticles to enhance plasmid DNA delivery to the nucleus is further not found persuasive because the claims do not recite methods of enhancing DNA delivery to the nucleus. The claims recites methods of transfecting dendritic cells comprising incubating dendritic cells with the transfection agent leading to the expression of an antigen. Any degree of expression would meet the limitations of the claims as written. Thus, the references are not required to provide a motivation or a expectation of success for enhancing delivery of the plasmid to the cell nucleus. Fattal et al. was cited to provide motivation for including a cationic detergent in a composition comprising a microparticle and a polynucleotide. In fact, Fattal et al. provides clear motivation for including a cationic detergent in a microparticle by teaching that inclusion of a cationic detergent in microparticles increases the amount of polynucleotide associated with the polymer particles and increases the uptake of the nucleic acid by phagocytosis. Thus, the skilled artisan would have been amply motivated to include a cationic detergent in a microparticle composition comprising a polynucleotide encoding an antigen in order to increase uptake of the polynucleotide by the target cell with a reasonable expectation that such uptake would result in expression of an antigenic protein encoded by the polynucleotide.

Furthermore, regarding the expectation of success for expression of a protein encoded by a polynucleotide adsorbed onto a cationic microparticle, it is noted that the state of the art at the time of filing establishes that many different methods are useful for introducing expression vectors into dendritic cells. The art further demonstrates that once in the cell, the vector expresses any encoded gene which is operably linked to appropriate expression elements, see for example Yang et al., Manickan et al., Spahn et al., and Tuting et al. (made of record by

examiner) cited as rebuttal evidence to arguments/evidence presented by the appellants in the office action mailed on 12/18/03. Thus, the state of the art at the time of filing supports the conclusion of the Office that the skilled artisan would have had a reasonable expectation that transfection of dendritic cells with a CTAB microparticle containing adsorbed polynucleotide encoding an antigen would result in expression of the encoded antigen in the transfected cells. In addition, both Song et al. and Hedley et al. provide specific examples of gene expression after the uptake of expression vectors via different routes such as introduction by viruses, liposomes, and microparticles. As a result, the skilled artisan would reasonably expect that successful delivery of an expression vector into a cell would be followed by gene expression. Since Fattal et al. demonstrates the successful delivery of nucleic acid into cells using particles containing cationic detergents, the skilled artisan would therefore have had a reasonable expectation of success that delivery of expressible nucleic acids using the same technique would in fact result in gene expression. As such, applicant's arguments are not found persuasive.

The appellant then argues that the particles taught by Fattal et al. are nanoparticles, not microparticles as claimed, or as taught in Hedley. In response, please note that the claim 54 as written clearly encompasses the same size particles as taught by Fattal et al., see for example instant claim 30 which depends on independent claim 1 and recites that the microparticles have diameters ranging from "about 500 nm to about 30 um". Thus, the question of "microparticles" or "nanoparticles" appears to be in part a question of semantics as the "microparticles" of the instant claims clearly encompass particles of "about 500 nm". Note as well that the term "about" is relative and as such "about" 500 nm reads on particles which are less than 500 nm. Thus, "nanoparticles" and "microparticles" clearly encompass particles of the same size including

particles less than 500nm. Furthermore, Fattal et al. teaches particles which are "about" 500nm in diameter. Appellants acknowledge this in their brief and in fact point to US Patent No. 4,489,055 (1984), Courvreur et al., as evidence that the procedure for producing nanoparticles used by Fattal et al. produces particles between 300-500nm. The compositions of microparticles taught by Hedley et al. also include particles of about 500nm, see for example Figure 2 of Hedley et al. Thus, both references, Hedley et al. and Fattal et al., regardless of semantics, teach particles that meet the claim limitations in terms of size.

The applicant further argues that because of the alleged size difference in the particles taught by Hedley et al. and those of Fattal et al., the Fattal et al. particles would not be phagocytosed, and thus there would be no motivation to combine the teachings of Fattal et al. with Hedley et al. In response, the prior art, including the Mukherjee et al. reference provided by applicants in their response filed on 12/14/04, teaches that cells use several different methods to uptake foreign matter, including phagocytosis and endocytosis. The claims as written do not include any limitation as to the mechanism by which the microparticles enter the dendritic cells. At the time of filing, particles of many different sizes were known to be successfully taken up by cells. In fact, both Hedley et al. and Fattal et al. demonstrate successful uptake of particles of different sizes comprising nucleic acids by cells. Thus, the art of record shows that both particles less than 1 um and particles greater than 1 um can successfully deliver nucleic acids into cells. Furthermore, please note that Fattal et al. does in fact teach that the nanoparticles are taken up by cells via an endocytic/phagocytic pathway (Fattal et al., page 137, abstract). In addition, and as stated in the previous office actions, Fattal et al. provides motivation to include cationic detergent in particles for nucleic acid delivery by teaching that the inclusion of cationic detergent

increases the amount of polynucleotide associated with the particles and increases the cellular uptake of these particles by cells.

Finally, the appellant argues that the skilled artisan would not be motivated to use cationic detergents with biodegradable microparticles because cationic detergents may impart stickiness to the resulting microparticles or have increased toxicity compared to nonionic detergents. However, since Fattal et al. actually teaches biodegradable microparticles with a cationic detergent and the successful use of the particles to deliver nucleic acid to cells, applicant's concerns about whether the skilled artisan would be motivated to combine a cationic detergent and a microparticle are moot. Fattal et al. already teaches just that combination. In fact, as noted above, Fattal et al. provides clear motivation for including a cationic detergent in a microparticle by teaching that inclusion of a cationic detergent in microparticles increases the amount of polynucleotide associated with the polymer particles and increases the uptake of the nucleic acid by phagocytosis.

Therefore, for reasons of record as discussed in detail above, appellant's arguments have not been found persuasive in overcoming the rejection of claim 54.

2) The appellant argues that claims 1-16, 18-23, 29-31, 33-44, 46, 50, 52, and 53 are non-obvious over the cited references, for the same reasons that claim 54 was argued to be non-obvious. The appellant then provides an substantially abbreviated version of the same arguments made against the rejection of claim 54. These arguments regarding the teachings of Song et al, Hedley et al., and Fattal et al. have been addressed in detail above in section **1)** in regards to independent claim 54. These arguments were not found persuasive for reasons discussed in detail

above and as they apply equally to the rejection of independent claim 1, and dependent claims 2-16, 18-23, 29-31, 33-44, 46, 50, 52, and 53, have not been found persuasive in overcoming the rejection of these claims either.

The appellant provides a single new argument concerning the rejection of claim 1 and its dependent claims. The appellant argues that unlike claim 54, claim 1 recites that the transfection agent is "..formed by a process that comprises: (a) providing microparticles comprising a biodegradable polymer and a cationic detergent, and (b) exposing said microparticles to said polynucleotide.." According to appellants, Fattal et al. does not teach adding polynucleotides to particles comprising a biodegradable polymer and the cationic detergent. The Office disagrees with applicant's description of the teachings of Fattal et al. On page 138, Fattal et al. clearly teaches that the oligonucleotide is added to a suspension comprising microparticles and CTAB (Fattal et al., page 138, column 2, paragraph 2). Due to the dynamic process of the association with cationic detergents the suspended microparticles, at least some portion of the particles taught by Fattal et al. comprise CTAB before they further associate with the polynucleotide. Furthermore, it is noted that the limitation regarding the process by which the transfection agent is made is not set forth as actual method steps in the method of transfecting cells as claimed. Rather, the appellant has included a product by process limitation in their method of transfecting cells. As such, while the Office does find that Fattal et al. does in fact teach the referred to process for making the transfection agent used in the claimed methods, it can also be argued that the process used to prepare the transfection agent is irrelevant as the patentability of method of using the product does not depend on its method of production. Note that if a product in a

product-by-process claim is the same as or obvious from a product of the prior art, the claim is unpatentable even though the prior product was made by a different process." *In re Thorpe*, 777 F.2d 695, 698, 227 USPQ 964, 966 (Fed. Cir. 1985) (citations omitted).

Therefore, for reasons of record as discussed in detail immediately above and in section **1)**, appellant's arguments have not been found persuasive in overcoming the rejection of claims 1-16, 18-23, 29-31, 33-44, 46, 50, 52, and 53.

3) The appellant argues that claims 19-23 are non-obvious for all the same reasons that claim 54 and claims 1-16, 18-23, 29-31, 33-44, 46, 50, 52, and 53 are non-obvious, and further because in their opinion, none of Song et al., Hedley et al., or Fattal et al., teach the administration of dendritic cells that have been transfected *ex vivo* with the claimed transfection agent to a subject. In response, the arguments regarding the teachings of Song et al, Hedley et al., and Fattal et al. as they apply to claim 54 have been addressed in detail above in section **1)** and in section **2)** as they apply to the rejection of independent claim 1, and dependent claims 19-23. These arguments were not found persuasive for reasons discussed in detail above.

In regards to the new argument that none of Song et al., Hedley et al., or Fattal et al., teach the administration of dendritic cells that have been transfected *ex vivo* with the claimed transfection agent to a subject, the appellant is directed to Song et al. As set forth in the rejection of record, Song et al. teaches methods of transfecting dendritic cells *ex vivo* or *in vitro* with a gene delivery vehicle comprising DNA encoding an antigen such as a tumor antigen, a viral antigen and specifically an HIV antigen, or an antigen derived from fungi, parasites, or bacteria, and use of said transfected dendritic cells to induce an immune response against the expressed

antigen *in vivo* (Song et al., pages 2, 3, and 18-20). Song et al. teaches that the transfected dendritic cells can be administered to a vertebrate parenterally or by direct injection, (Song et al., pages 26 and 39). Thus, Song et al. provides the specific teachings to administer dendritic cells that have been transfected *ex vivo* to a subject for the purpose of inducing an immune response. Hedley et al. and Fattal et al. were cited for providing teachings and motivation to utilize a transfection agent comprising a polynucleotide adsorbed onto the surface of a microparticle comprising a biodegradable polymer and a cationic detergent over the cationic liposomes and plasmids or cationic lipids and plasmids taught by Song et al. Further, appellants contention that Song et al. expresses a clear preference for direct injection of recombinant retroviruses over *ex vivo* techniques, has already been addressed in section **1)** above, which stated that although Song et al. may have exemplified retroviral transduction of dendritic cells, and stated a preference for the use of *in vivo* transfection of dendritic cells, neither of these teachings invalidates the clear teachings in this reference that many techniques, including non-viral techniques, can be used to transfect dendritic cells *in vitro*, or that the dendritic cells can be transfected *ex vivo* and then administered to the subject. It is reiterated that a reference must be considered not only for what it expressly teaches, but also for what it fairly suggests. *In re Burkel*, 201 USPQ 67 (CCPA 1979). Further, the appellant is again directed to *In re Susi* and *In re Gurley*, which state respectively: that disclosed examples and preferred embodiments do not constitute a teaching away from a broader disclosure or nonpreferred embodiments. *In re Susi*, 440 F.2d 442, 169 USPQ 423 (CCPA 1971).

Therefore, for reasons of record as discussed in detail immediately above and in section **1)** and **2)**, appellant's arguments have not been found persuasive in overcoming the rejection of claims 19-23.

In conclusion, the rejection of claims 1-16, 18-23, 29-31, 33-44, 46, 50, and 52-54 under 35 U.S.C. 103(a) as being unpatentable over WO 97/24447 (7/10/97), hereafter referred to as Song et al., in view of US Patent No. 5,783,567 (7/21/98), hereafter referred to as Hedley et al., and further in view of Fattal et al. (1998) J. Controlled Rel., Vol. 53, 137-143, is maintained.

(11) Related Proceeding(s) Appendix

No decision rendered by a court or the Board is identified by the examiner in the Related Appeals and Interferences section of this examiner's answer.

For the above reasons, it is believed that the rejection should be sustained.

Respectfully submitted,

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